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Neurodevelopmental outcomes in children with liver diseases: a systematic review

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Abbreviations:

ADHD: attention deficit and hypersensitivity disorder

ALF: acute liver failure

BA: biliary atresia

LTx: liver transplantation

Abstract

Objectives: To determine the neurodevelopmental outcomes of children with liver diseases based on a systematical review of the literature.

Method: a literature search according to the PRISMA statement was conducted using predefined search terms in PubMed, Cochrane Library, and PsycINFO. The inclusion criterion was studies published from 2000 onwards that reported on the neurodevelopmental outcomes of term-born children with liver diseases. A narrative synthesis was done to appraise the studies.

Results: Twenty-five studies were included (1913 children), 19 of which described children after liver transplantation (LTx) (1372 children). 67% of the studies on children with liver diseases who survived with their native livers showed low-average or abnormal scores on specific subscales of cognitive and behavioral measures. In studies on children after LTx, this was 82%. After LTx, 83% of studies demonstrated impaired outcomes on behavior, while 42% of children received special education. Motor development was impaired in 82% of studies in children with native liver and after LTx.

Limitations: Studies were heterogenic due to sample sizes, aetiology of liver disease and type of assessment tools used.

Conclusions: More than two-third of included studies showed neurodevelopmental deficits in children with liver diseases, affecting all neurodevelopmental areas.

Knowledge on risk factors for impaired neurodevelopment is limited and lack of long term follow-up is worrying, especially considering the increasing survival rates, resulting in more at risk patients. Studying early predictors and risk factors of abnormal

developmental trajectories of children with liver diseases is indicated to assess strategies to improve their long-term neurodevelopmental outcomes.

What is known:

- Treatment possibilities for children with liver diseases have improved over the last decades which has led to increased survival
- Children with liver disease are at increased risk for impaired neurodevelopment before and after liver transplantation (LTx)

What is new:

- Children with liver diseases are at increased risk of deficits in all neurodevelopmental domains: cognitive, behavioral and motor outcome
- During follow-up of children with liver diseases special attention to neurodevelopment is warranted
- Relatively little is known on neurodevelopmental outcomes in children with liver diseases with their native livers compared to children after LTx

Introduction

The structural morphology of the brain is well-established at birth, while vital functional maturation continues postnatally.(1) Intellectual functioning and motor development develops rapidly during the first years of life and this maturation is influenced by neuronal input, such as environmental and experiential factors.(1) Nevertheless, several pediatric patient groups are known to be at risk of neurodevelopmental delays during this period. Early risk factors for neurodevelopmental delays in children include preterm birth and subsequent intensive neonatal care, complications during birth, infections, unconjugated hyperbilirubinemia, anesthesia, major surgery, malnutrition, growth restriction, and environmental deprivation.(2–5) Accordingly, severe disease, hospitalization, and surgery during early childhood are also thought to interfere with the healthy development of children's central nervous systems.

Infants with congenital liver diseases are often exposed to one or more of the above risk factors. Previous studies primarily explored the influence of liver transplantation (LTx) on neurodevelopmental outcomes.(6–9). The outcomes, however, of children with liver diseases prior to LTx might already be impaired due to existing morbidities.(3,9,10) To date, the exact interaction or role of risk factors on neurodevelopment is not yet fully delineated. As survival rates are increasing, it is essential to explore the possible adverse consequences of early liver diseases, in order to grow up to productive, independent young adults.

Our aim was:

- to determine the neurodevelopmental outcomes of children with liver diseases based on a systematical review of the literature.

- to identify neurodevelopmental deficits and related risk factors in children with liver diseases, both in children with liver diseases who survived with their native livers and after LTx, in order to identify fields of neurodevelopment that are most affected and that could possibly benefit from intervention programs at an early stage.

Methods

The study protocol was registered with PROSPERO, the international prospective register of systematic reviews, under number CRD42016039074. Studies on the neurodevelopmental outcomes in children with liver diseases were retrieved from PubMed, the Cochrane database, and PsycINFO from January 1, 2000 until March 31, 2017 and structured literature search was performed according to the PRISMA statement. The following predefined search terms were used: infant, newborn, child, youth; liver disease, liver failure; cognition disorders, psychomotor disorders, problem behavior, neurodevelopment, developmental outcome, learning disorder, IQ, motor outcome, neuropsychology, psychomotor, and the different etiologies of liver diseases, as described in our research protocol.

All articles were screened independently and blindly by three authors (LHR, JLB, and AEDH). Firstly, one author (LHR) screened all articles on title and abstract. Similarly, the other two authors (JLB and AEDH) both blindly screened half of the articles. After the initial search, duplicates and articles published before 2000 were excluded and articles were screened on title and abstract. In case of a discrepancy the three authors discussed the matter until consensus was reached. In addition to the articles found through the literature search, the reference lists of the included studies were examined to identify possible additional studies eligible for inclusion.

Inclusion criteria were: studies that reported on liver diseases in childhood and described neurodevelopmental outcomes of children with respect to cognition, social-emotional, behavioral and motor functions were included. Only studies that used standardized tests or validated questionnaires were included. Studies eligible for

inclusion described term-born children aged between 0 and 18 years. Exclusion criteria were: articles not written in English, or when they did not match domain, determinant or outcome, i.e. when they did not use standardized tests or validated questionnaires. Studies that did not describe the etiology of liver diseases were also excluded. All types of study designs were included, except reviews, case series and case reports on fewer than ten cases, abstracts, posters, and books.

A narrative synthesis was conducted and the following data extracted from the included articles: study design, duration of follow-up, types of liver disease, patient characteristics, assessment tools, neurodevelopmental domains, cognitive, behavioral and motor outcomes, and possible risk factors for neurodevelopmental impairments. Also, data on school performance was extracted from the articles. In order to obtain a clear overview of the differences between studies in children with their native livers and studies in children after LTx, these studies were displayed separately. In LTx studies age at LTx, duration of follow-up after LTx, and whether the donor liver came from a living or a deceased donor was also included.

Table 1 and 2 display information on the included studies: study design; participants; etiology of liver disease; used assessment tools; cognitive, behavioral and/or motor outcomes and risk factors for impaired neurodevelopmental outcomes. When classifying in borderline and abnormal neurodevelopmental scores, included studies used cut-off values following the criteria of test manuals (e.g. for the WISC, cut-off values for IQ were < 85 for borderline IQ (-1SD) and < 70 for abnormal IQ (-2SD)).

Results

Figure 1 shows the inclusion chart. After literature search 1276 related publications were included. Ultimately, upon analysis of eligibility, 25 papers were included amounting to 1913 patients with liver diseases, of whom 541 not-transplanted and 1372 transplanted children. Table 1 and 2 provide a detailed overview of the included studies.

All studies described neurodevelopmental outcomes in children with liver diseases of different underlying etiologies. Nineteen of these studies were on children after LTx. The children who participated in the various studies represented a heterogeneous group of liver diseases, such as viral hepatitis, metabolic etiologies, biliary atresia, and liver tumors. The number of patients varied between 11 and 823 children. Control groups were used in 11 studies.

All of the used test batteries and questionnaires were validated and internationally accepted. There was a high diversity in used test batteries and questionnaires, all displayed in Table 1 and 2. To assess cognition, mostly used were versions of the Wechsler Intelligence Scales (WISC), i.e. in 14/23 studies, according to different age categories. For behavioral outcome and executive function the following assessments were predominantly used: Child Behavior Checklist (CBCL) in 4/13 studies and Behavior Rating Inventory of Executive Function (BRIEF) in 6/13 studies respectively. Motor outcome was assessed with Mullen Scales of Early Learning (MSEL) in both studies assessing motor outcomes in children with native liver disease. In children after LTx, the most used test was the movement ABC.

The neurodevelopmental outcomes of children with liver diseases who still had their native livers

Table 1 provides an overview of the neurodevelopmental outcomes of children with liver disease who still had their native livers. In children with viral hepatitis and hepatic encephalopathy due to acute liver failure, significantly lower scores on cognition tests were observed, both in acute and under more chronic conditions (IQ (mean \pm SD) 61.8 ± 13.6 in children with chronic viral hepatitis vs 106.2 ± 12.8 in controls).(11,12) The results of children with acute liver failure normalized during follow-up, approximately five months after discharge, when the hepatic encephalopathy resolved.(11) Children suffering from chronic viral hepatitis, with normal liver function tests, obtained lower scores on vocabulary, total verbal relation, the bead memory test, total short-term memory, and IQ, in comparison to healthy controls.(12) In other studies, children with viral hepatitis showed neither impaired outcomes on cognitive tests, nor differences in behavioral outcomes in comparison to the norm population or uninfected controls (i.e. IQ mean 103.9).(13,14)

In children with biliary atresia (BA), who were being evaluated for LTx, lower scores on cognitive outcomes were reported in comparison to the norm population (visual reception 89.90 ± 8.42 , expressive language 90.60 ± 19.91 , receptive language 79.90 ± 13.25 compared to norm scores with a mean of 100).(10,15) Motor development was also impaired in children with BA (gross motor 71.80 ± 13.14 , fine motor 94.53 ± 19.80 compared to norm scores with a mean of 100).(10,15) Thus far, no studies have been published on behavioral outcomes in children with BA, without LTx.

School performance (% special education or repeated classes) was not reported in studies on children with liver diseases who still had their native livers.

The neurodevelopmental outcomes of children after liver transplantation

Table 2 provides an overview of the studies on the neurodevelopmental outcomes of children with liver diseases after LTx. In most studies on children after LTx, intelligence scores were below the average of the norm population, but still fell within the average range (i.e. FSIQ 86.6-98).(9,16–24) Kaller and colleagues found that all scores on cognition abilities fell in the low-average range in children at least one year after LTx. Almost 10% of these children had an abnormal total IQ (<70) in comparison to 4.7% of their healthy peers. Furthermore, 16% of children with liver diseases scored within the borderline IQ range (70-84) in comparison to 6% of their healthy peers.(18) In the subcategories of the cognitive tests, such as attention abilities, executive functioning, visuospatial functioning, and language development, the mean scores fell within the average range, but below the population mean (Table 1 and 2).(6–8,15,17,19,20,23,25,26) Moreover, Sorensen and colleagues found no improvement in cognition after LTx, only reading was likely to improve.(20) Stevenson and colleagues found, in their longitudinal cohort, impaired cognitive outcomes pre-LTx and a significant decrease at three months post-LTx.(9) At one year post-LTx the scores had returned to the pre-LTx level with no further improvement at two years after LTx.(9)

Children receiving LTx for liver diseases showed more total behavioral (12% borderline scores, 32-50% abnormal) and externalizing problems (4-31.2% borderline scores, 32-31.2% abnormal) in comparison to the norm population or in comparison to children with stable chronic liver diseases.(7,19,27)

Motor outcomes were impaired in children with LTx in comparison to healthy children.(6,28) Almaas and colleagues found in their longitudinal cohort with 4 year follow-up no improvement in motor scores with time after transplantation.(28) In contrast,

Van Mourik and colleagues found that individual motor scores improved gradually after LTx and reached the average range within four years after LTx.(29) In metabolic patients, psychomotor functions were delayed at -2 SD before transplantation.(9) The scores of patients who had received a transplant at less than 42 months of age, improved over 2 years of time to the low-average range.(9)

School performance was reported in 8/19 studies on children with liver disease and LTx. Of included children, up to 42% needed special education and 6-55% had repeated one or more classes at school (Table 2).(8,9,16,19,22,23,30,31)

Children with liver diseases before or after LTx show impairments on all domains of neurodevelopment in comparison to the general pediatric population. Although the mean subscores often fall within the average range, the shift in distribution to lower scores implies that a larger fraction of children have abnormal scores at individual level.

Risk factors associated with neurodevelopmental outcomes

In Table 1 and 2 an overview is provided of risk factors for neurodevelopmental impairments in children with liver diseases. Cognitive outcomes in children with liver diseases before and after LTx were negatively correlated with low weight and height z-scores at the time of surgery (Kasai hepatoportoenterostomy or LTx) (8,10,15,20,21,26), age at LTx, blood transfusion volume during LTx, days spent in hospital less than one year post-LTx, and number of pre-LTx, peri-LTx, and post-LTx complications. (7,8,17,20,26) Also, in a multi-center study, one-person households were associated with impaired cognitive outcomes.(20) Some studies performed multiple regression analysis and reported higher scores on late postoperative (between three and ten years) achievement scales in patients who had a living-related donor in comparison to a cadaveric organ.(8,26) In children with viral hepatitis and hepatic encephalopathy due to acute liver failure, cognitive test results were negatively correlated to elevated blood pro-inflammatory cytokines and liver changes on MRI.(11,12) Furthermore, more impaired scores on cognition were reported in children after LTx for genetic-metabolic induced liver disease in comparison to children after LTx with BA or other cholestatic diseases, both before LTx and during follow-up.(9,18,21)

Risk factors for impaired motor outcomes in children with liver diseases were impaired nutritional status peri-LTx, shorter disease period before LTx, and LTx at older ages. (23,29)

Concerning school performance, the most striking risk factor for special education post-LTx was requirement for special education pre-LTx.(31) Use of calcineurin inhibitors or cyclosporine/other non-calcineurin inhibitor based immunosuppression was associated with impaired scores on cognition and special education.(21,31)

Discussion

The aim of this systematic review, executed in accordance to the PRISMA guidelines, was to provide an overview of the current literature on the neurodevelopmental outcomes in children with liver diseases who still had their native livers and/or after LTx and to identify possible risk factors for impaired outcomes. The treatment possibilities of children with liver diseases have improved significantly over the last decades and survival rates are increasing, making it a chronic rather than a fatal disease. It is therefore essential to gain insight into the long-term sequel of liver diseases in childhood.

All studies reported deficits in one or more areas, be it in the cognitive, motor, or behavioral domains. The majority of the studies reported cognitive deficits in children with liver diseases with their native livers (4/6 studies; 67%) and in children after LTx (14/17 studies; 82%). In children with their native livers, as well as after LTx, low IQ scores were the most predominant outcome. All studies in children surviving with their native livers, and most studies including children after LTx, showed low-average and significantly abnormal scores on subscales of cognitive and behavioral measures. Also, a remarkable percentage of children after LTx received special education or had already repeated one or more classes (up to 42%). Of nine studies describing motor outcomes, seven described impairments in one or more subtests of motor development (82%). The two other studies described average scores on motor development, with slightly higher scores in children with native livers compared to children after LTx.(24) Remarkably, there are more studies on neurodevelopmental outcomes in children with LTx compared to children with liver diseases who still had their native livers. There is little to no data on

behavioral outcomes nor on school performance of children with liver diseases who still had their native liver.

Factors that appeared to be associated with neurodevelopmental outcomes were variable to some extent. The impaired neurodevelopmental outcomes in children with liver diseases without LTx or before LTx suggest that a liver disease itself influences neurodevelopment, which might or might not be aggravated by surgical therapy and its sequelae. Gilmour *et al.* showed that children at highest risk for special education post-LTx were those who already received special education pre-LTx or those who were too young and not yet in school at time of LTx. This suggests that neurodevelopmental deficits were, to some extent, already present before LTx. Etiology of liver diseases plays an important role in neurodevelopmental impairment. Cognitive outcomes were more impaired in children with metabolic disorders than in children with BA or other cholestatic diseases. We have to bear in mind that in some liver diseases, for example, the metabolic induced liver diseases, impaired neurodevelopment might be explained by brain damage due to the underlying disease. Poor adherence to therapy could also influence neurodevelopmental outcome in certain liver diseases.(21) In some children with liver failure, either acute or chronic, the neurodevelopmental deficits recovered following adequate treatment and LTx.(11) This is in line with previous studies that reported improvement in neurodevelopment after LTx.(3,32) Results on whether motor outcomes improved over time after LTx were inconsistent; two studies showed improvement after LTx and one study did not.(9,28,29)

Other studies showed that LTx itself is an important contributory factor to neurodevelopmental impairment.(19,24,27) Nevertheless, Stevenson and colleagues showed that negative effects of LTx on neurodevelopment can be reversible within one

year after LTx.(9) The factor most associated with neurodevelopmental outcome was growth failure at the time of LTx. Growth failure might be caused by malnutrition which, in early childhood, is associated with dendritic spine abnormalities, short apical dendrites, fewer spines and altered neurotransmitter function and responsiveness.(33) Recently Lurz *et al.* showed that children with end-stage liver disease had a significantly lower psoas muscle surface area when compared to age-matched healthy controls. This suggests an impaired nutritional status in children with end stage liver disease.(34) Improved nutritional status peri-LTx was associated with increased muscle bulk and subsequent improvement in motor scores.(29) Based on current data, nutrition seems to be the only risk factor amenable to a short-term potential intervention to improve neurodevelopmental outcome.

The effect of general anesthesia in early childhood on neurodevelopment is still unclear. Numerous cohort studies found conflicting evidence for an association between exposure to general anesthesia and neurodevelopmental outcomes.(35–37) To the best of our knowledge the association between general anesthesia and neurodevelopmental outcome in children with liver diseases has not been investigated yet. Furthermore, exposure to general anesthesia was not found as a risk factor for impaired neurodevelopmental outcome in the included articles of this review.

In one of the multi-center cohort studies, Gilmour *et al.* showed that both treatment with calcineurin inhibitors and with non-calcineurin inhibitors post-LTx was associated with impaired cognitive outcomes and special education.(21,31) Calcineurin inhibitors and non-calcineurin inhibitors, as well as exposure to steroids at young age, are known for its neurotoxicity.(38–40) More research is needed to explore the potential risk of immunosuppressive regimens post-LTX for neurodevelopmental impairments.

Other factors associated with impaired neurodevelopmental outcomes concerning LTx were younger age at LTx and longer duration of hospitalization. Studies on children with BA showed that younger age at LTx is associated with better cognitive development. (8,10,15,18,23,26) This might be due to a better nutritional status and growth, shorter exposure to the liver disease and earlier normalization of toxic liver values after transplantation at a younger age, possibly also at an age period in which the brain has higher plasticity to adapt. Other studies showed that children who underwent transplantation in the first six months after birth have more impaired neurodevelopmental outcomes in comparison to controls or the norm population.(3,17,41) The children who underwent LTx before the age of six months are predominantly children with BA with insufficient therapeutic effects of hepatoportoenterostomy (Kasai procedure) necessitating LTx at this young age. It is tempting to speculate that the worse outcomes in these children are due to the underlying liver disease and not to the surgical intervention per se.

Our conclusion is that this review shows that children with liver diseases are prone to neurodevelopmental impairments. The studies included in this review show that children with liver diseases are at risk of deficits in all areas of neurodevelopment, i.e. cognition, behavior, and motor development. Even though the mean scores predominantly fall within the average range, most scores are lower than scores in the norm population or control groups. Moreover, it is obvious that a remarkably larger number of children have abnormal scores on neurodevelopment when compared to control groups or norm population. The limited number of studies in this field suggests that this population is struggling in growing up to productive, independent young adults. It might be that both adequate medical and/or surgical treatment of liver diseases and

more 'aggressive' nutritional management contribute to better neurodevelopmental outcomes. Both are of great practical importance in the day-to-day lives of children and their families who experience many problems because of neurodevelopmental impairments. Furthermore, the findings emphasize that special attention to neurodevelopmental sequelae in children with liver diseases needs to be given during follow-up and possible intervention programs with neuropsychologists, physiotherapists, and rehabilitation consultants are warranted. Unfortunately, it is difficult to investigate neurodevelopmental outcomes in homogenous groups of adequate sample sizes, as pediatric liver diseases are (relatively) rare. In consequence, the knowledge gap is worrying, especially when one takes into consideration that survival rates are improving and that as a consequence the number of at-risk patients is increasing. We believe that this patient group might benefit from intervention programs in analogy to preterm infants. Previous research in preterm born infants has shown the benefits of an early intervention program to improve neurodevelopmental outcomes.(42,43) However, liver disease often is a more chronic condition. Research is needed to explore the potential benefits of neurodevelopmental intervention programs to improve long-term outcomes in children with liver disease. This systematic review forms the basis for a prospective study that should provide more insight into the steps that have to be taken to improve neurodevelopmental outcome in children with liver diseases.

Limitations

Even though there was a reasonable overlap in the findings of the studies described in this review, there were notable differences too. These differences are probably due to the heterogeneity of the studies and in the types of liver diseases.

Sample sizes in the majority of the studies were small. Due to the nature of retrospective cohort studies, confounders may have biased results on risk factors of deficits. As presented in Table 1 and 2, studies were highly divergent with respect to:

1. Target population, in sense of age of patients (0-18 years) and etiology of liver diseases (over 30 different etiologies).
2. Measurement of outcomes, i.e. 28 different test batteries and questionnaires were used to measure cognition, behavior and/or motor outcome.

Given these differences in applied design and methods, the outcome per each outcome (cognition, behavior and motor outcome) from one study may not be the same as in the other included studies. This hinders comparability of results across studies and hence a meaningful statistical analysis of combined results becomes infeasible. Well-designed randomized controlled trials are essential for more reliable results.

Future implications

We conclude that children with liver diseases are at increased risk of deficits in one or more areas of neurodevelopment be it in the cognitive, motor, or behavioral domains. In our opinion, adequate long-term follow-up studies to investigate the developmental trajectories of children with liver diseases are urgently required. Future research is necessary to determine early predictors and risk factors, and to explore the possibilities with regard to interventions that could eventually improve the long-term neurodevelopmental outcomes in order to support these vulnerable patients in growing up to productive, independent young adults.

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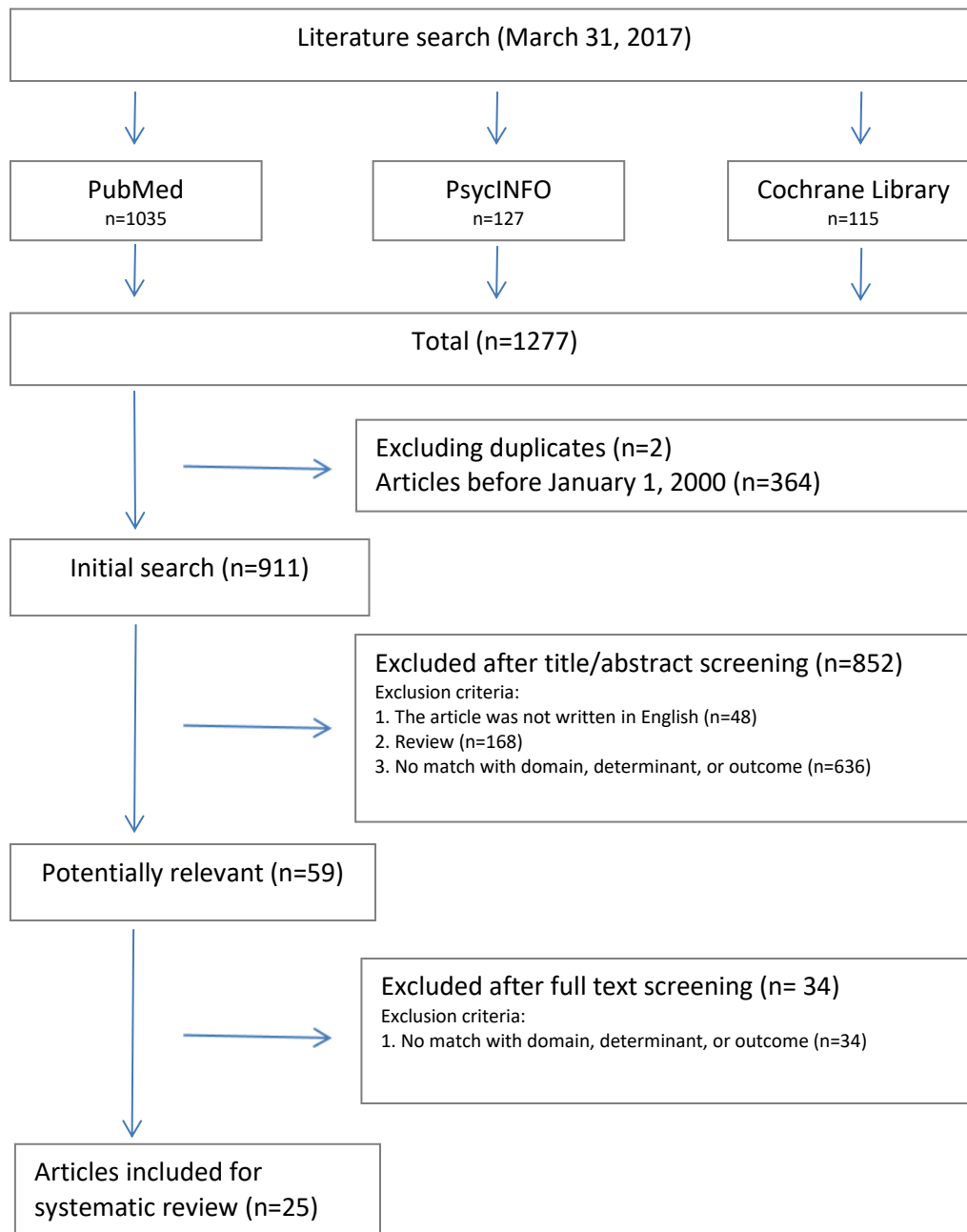


Figure 1. Flow chart of the literature search